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--17. A method for stimulating a cytotoxic T cell response in an animal comprising introducing into said animal a cytotoxic T cell response stimulating amount of the composition of claim 1.--

--18 A method for stimulating a γ- interferon response in an animal comprising introducing into said animal a γ- interferon response stimulating amount of the composition of claim 1.--

REMARKS

After giving effect to the amendment to the claims herein, Claims 1-7, and 10-18 are pending in this application. Initially, Applicants wish to thank the Examiner for her careful and considered review of the subject application. In response to the Examiner's request, a substitute specification is enclosed pursuant to 37 C.F.R. §1.125 (MPEP 608.01(q)). No new matter has been added, each page of text appears on single-sided paper rather than double-sided as originally filed. In addition to amending the informalities pointed out by the Examiner at page 2, item 15 of the instant Office Action, Applicants have corrected additional informalities based on an independent review of the subject application. In correcting these inadvertent errors, Applicants have not added any new matter to the specification but have merely clarified meaning of the specification based on the subject matter disclosed at the time of filing.

One procedural point requires clarification. At the time Applicants entered the national phase of prosecution of this application, 23 December 1994, a preliminary amendment amending claims in conformance with U.S. practice was submitted. Because in the Office Action mailed 24 July 1994, the Examiner did not indicate that the preliminary communication had been considered, Applicants

are unsure as to which claims have been examined. Clarification is respectfully requested.

Before the issues raised by the Examiner are substantively addressed, Applicants believe a brief description of the subject invention may be useful. The subject invention relates to a unique and highly effective adjuvant combination. While the term "pioneering" is often over used, the subject invention clearly falls into this class. The adjuvant system disclosed and claimed herein will likely form the basis for a new generation of therapeutic vaccines. While commercial activity is not required to establish the patentability of an invention, its evidence serves as one indicia of the practical utility of the discovery. SmithKline Beecham Biologicals certainly considers the subject invention useful as evidenced by the establishment of an entire new company SB Biologicals Immunotherapeutics to develop QS21/3D-MPL-based vaccines and to oversee the numerous clinical trials now ongoing and about which more will be said below.

As claimed, the vaccines of the subject invention require three distinct components: (a) an immunogen source in the form of an antigen, antigen composition or combinations thereof; (b) QS21 and (c) 3D-MPL. This unique combination, neither disclosed nor suggested by the prior art, results in an enhanced CTL response. Favorable consideration of the claims, as amended herein, drawn to this important invention is respectfully requested.

Rejections Under 35 U.S.C. §101:

Claims 8 and 9 are rejected under 35 U.S.C. §101 as being drawn to a non-statutory class of invention. Additionally Claims 8 and 9 are also rejected under 35 U.S.C. §112, second paragraph for failure to recite positive action steps for the uses claimed. In response to this rejection, Claims 8 and 9 have been canceled. Such action has rendered both rejections moot and the rejections should be withdrawn. Additional claims are presented herein to more specifically and distinctly claim the subject invention.

Claims 1-12 are also rejected under 35 U.S.C §101 as claiming the same invention as copending USSNs. 08/442,286 and 08/356,372. This rejection is considered provisional in that conflicting claims have not as yet been patented. These applications were filed as a part of Applicants' strategy to respond to the GATT implementing legislation passed by Congress. Upon notification of allowance of the claims in the 08/356,372 application, Applicants will cancel all conflicting claims in both this application and the '286 application.

Rejections Under 35 U.S.C. §112:

Claims 6, 8 and 9 are rejected under 35 U.S.C. §112, first paragraph, as allegedly being enabled only if limited to antigen compositions containing glycoprotein D and CS in combination with the claimed adjuvant system. Specifically, the Examiner raises concerns with respect to the HIV and FeLV embodiments of the invention. Although the rejection is cast as one of enablement, the reasoning offered by the Examiner seems to be predicated upon issues of utility. If the utility of the claimed invention is in question, the appropriate rejection under 35 U.S.C. §101 should be made, keeping in mind the Utility Guidelines recently promulgated by the USPTO in connection therewith.

In response to the enablement rejection of Claim 6 (the rejection of Claims 8 and 9 are moot in view of their cancellation herein), it should be remembered that objective enablement is all that is required. How such a teaching is set forth, whether by the use of broad terminology or working example, is irrelevant. In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1435 (Fed Cir. 1991). In assessing the question of enablement, it should be remembered the subject invention is predicated upon the surprising adjuvanting utility of a specific combination of two immunopotentiators which results in an increased CTL response to the eliciting antigen. Accordingly, in selecting illustrative test antigens, Applicants intentionally chose as examples a **particulate, insoluble** antigen, the malarial

antigen RTSS, and an antigen from the opposite end of the spectrum, a **soluble** antigen from HSV, rg D_2t. Given the teachings in the disclosure, as filed, one of ordinary skill in the art could, without undue experimentation and the exercise of inventive skill, employ the claimed adjuvant system with a particular antigen of choice with the expectation of an enhanced CTL response. It should be noted that there is no requirement that every antigen/adjuvant combination have the same degree of utility (In re Gardner, 475 F. 2d 1389, 177 USPQ 396 (CCPA 1973). In fact a broad claim may even contain some inoperable species, so long as the number of such species does not become excessive. Atlas Powder Co., v. E. I. duPont de Nemours and Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). Here by the judicious selection of an appropriate spectrum of antigen types, objective enablement has been clearly established. While Applicants maintain that the data in the specification, as filed, are sufficient to support the claimed invention, as pointed out above extensive development of antigen/adjuvant combinations are underway at SmithKline. Briefly, data are available in respect of the use of the claimed vaccines in both prophylactic and therapeutic Guinea pig models of HSV-2, a mouse influenza model and a Cotton rat model of Respiratory Syncytial Virus infection. Applicants reserve their right to file a Declaration under 37 C.F.R. §1.132 providing such data should the Examiner indicate that those results would be helpful in evaluating the patentability of the claimed invention.

With specific reference to the rejection as it relates to HIV, while clinical trials are proceeding, those results are still pending and are presently unavailable. The fact the trials are being permitted, is at least some evidence that the appropriate regulatory authorities acknowledge that a practical utility exists that is worthy of further evaluation. However, in order to advance the prosecution of this application, a new claim (Claim 13) is presented in which the HIV and FeLV embodiments have been deleted. If this claim is considered to be otherwise patentable, Applicants will then remove the HIV and FeLV embodiments from

this application and continue their prosecution separately in one or more of the existing continuing applications.

Claims 1-12 are rejected under 35 U.S.C. §112, second paragraph, as allegedly failing to distinctly claim the subject matter of the invention. Specifically, the meanings of the term "antigen", "antigen composition" and "combinations thereof" are said to be unclear. The rejection of Claims 1-12 under 35 U.S.C. §112, second paragraph is respectfully traversed. The meaning of the terms antigen, antigen composition and combinations thereof are believed to be clear to someone of ordinary skill in the immunological arts. An "antigen" has its ordinary immunological meaning of a substance capable of eliciting an adaptive immune response and can react specifically with the corresponding antibodies or T cell receptors. An "antigen composition" simply refers to an antigen as a part of some more complex composition of matter. For example, an antigen might be added to the adjuvant system of the subject invention covalently attached to a carrier which itself may or may not be antigenic. Alternatively, the antigen may be present as a preparation resulting from sub-cellular fraction or may be present as a component of a heat-killed or genetically attenuated pathogen. The term composition merely indicates the antigen in a form other than the antigen per se. "Combinations thereof" has its ordinary meaning that one or more antigens, one or more antigen compositions and/or one or more antigen and antigen compositions may be present as the immunogen when added to the adjuvant system of the subject invention.

In view of the amended claims and the arguments above, withdrawal of the rejection of Claims 6, 8 and 9 under 35 U.S.C. §112, first paragraph and withdrawal of the rejection of Claims 1-12 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejections Under 35 U.S.C. §103:

The subject invention, as discussed above, requires an immunogen source in combination with two adjuvanting entities, QS21 and 3D-MPL.

Claims 1, 2, 5, 6, 8, 10 and 12 are rejected under 35 U.S.C. §103 as unpatentable over Long et al. (Infection and Immunity 37 (2):761-764 (1984)) in view of Kensil et al. (U.S. Patent 5,057,540, Issued 15 October 1991) and further in view of Schneerson et al. (J. of Immunol. 147(7):2136-2140 (1991)). This combination of references is said to establish a prima facie case obviousness thus rendering the claims unpatentable under 35 U.S.C. §103. This is rejection is respectfully traversed. For the reasons given below, Applicants maintain that viewing the invention as a whole and without hindsight, the combination of references cited by the Examiner when taken in their entirety, fail to remotely suggest the invention as claimed and as such fails to establish a prima facie case of obviousness.

The Art Cited:

The primary reference, Long et al., discloses the use of HSV-1 or -2 Glycoprotein D as an immunogen capable of protecting mice against a subsequent lethal challenge of Herpes Simplex Virus. The potential of gD as a subunit vaccine is discussed. In all cases the gD antigen was formulated in Freund's complete adjuvant. Such an adjuvant is highly toxic and is not licensed for human or veterinary use. Only antibody (e.g., humoral) responses are described, no CTL effect is noted. There is no suggestion that an enhanced CTL response is desirable. There is no suggestion to use an adjuvant other the Freund's complete. There is no suggestion to use more than one adjuvant. It is also noted that in the concluding sentence that is remains to be seen if the test vaccine is protective against the establishment of latency or recurrent infection.

The secondary reference Kensil et al. discloses the use of saponins as adjuvants. This fact was noted by the Applicants in the subject application at page 1, line 14-16. The Kensil et al. patent does suggest, at col 7, lines 14-40, that saponins may be used in combination with one another or with non-saponin adjuvants, 3D-MPL is not among the suggested non-saponin adjuvants considered useful for practicing the Kensil et al. invention. Moreover there is no suggestion the QS21 (nee QA21) effect could be synergized by the addition of another adjuvant. As shown in the subject application, 3D-MPL alone had no effect on the CTL response but enhanced the QS21 effect by over 3 fold. It is interesting to note that with respect to the Kensil et al. patent, a single working example was found to be sufficient to support broad method and composition claims, not limited to a particular antigen.

The tertiary reference Schneerson et al. relates to MPL not 3D-MPL. The only combination taught by Schneerson is MPL with trehalose dimycolate (TDM) a cell wall extract of a mycobacterium. There is no suggestion that other adjuvants should be used. Indeed TDM appears to be essential, since MPL on its own does not appear to be effective.

The combination of references cited is improper

and legally insufficient to establish the prima facie case of obviousness.

The Examiner has selected a combination of three references from which it is concluded the subject invention was obvious. For the factual reasons presented above, the combination of references is insufficient to render the claimed invention obvious. It should also be noted that it is clear that in order to establish a background for finding obviousness under 35 U.S.C. §103 that the determination of the scope and contents of the prior art cannot be performed by the mere gathering of elements from separate and distinct disclosures irrespective of the teachings of the disclosures. As stated by the CCPA In re Imperato, 179

U.S.P.Q. 730 (C.C.P.A. 1973) "...the mere fact that those disclosures can be combined does not make the combination obvious unless the art also contains something to suggest the desirability of the combination (emphasis is original; citation omitted)." There must be a reason apparent at the time the invention was made or the references and the use of such teachings as evidence of obviousness will entail prohibited hindsight. In re Nomiya, 184 U.S.P.Q. 607 (CCPA 1975). One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fine, 5 U.S.P.Q. 2d. 1596 (Fed. Cir. 1988). The law is overwhelmingly clear on the point of combining references in support of a §103 rejection: unless there is some suggestion in the art of the desirability of combining the elements of the individual references, the references cannot be combined by the Examiner to support his contention of obviousness. In re Wesslau, 353 F.2d 238, 147 U.S.P.Q. 391 (CCPA 1965); In re Lamm 172 U.S.P.Q. 278 (CCPA 1972); In re Imperato, 179 U.S.P.Q. 730 (CCPA 1973); In re Bergel and Stock, 292 F.2d 955, 130 U.S.P.Q. 206 (CCPA 1961); In re Rothermel, 276 F.2d 396, 125 U.S.P.Q. 328 (CCPA 1960); Fromson v. Advance Offset Plate, Inc., 225 U.S.P.Q. 26 (Fed. Cir. 1985).

Here, the Examiner has garnered an immuogenic element from one teaching that is completely silent with respect to the use of the dual adjuvants of the claimed invention, one adjuvant element from a second reference that fails to teach the use of the specifically claimed second adjuvant and a third reference which fails to teach the second adjuvant of the claimed invention but apparently teaches the ineffective use a chemically related compound. There is nothing save the prohibited hindsight gained from reading applicants' own disclosure that would suggest the combination constructed by the Examiner. In its most recent consideration of the law of obviousness the Federal Circuit clearly counsels against placing the de facto placing of the applicants' own disclosure into the prior

art to support to support a rejection under §103 based on a combination of references. In re Ochiai, 1995 U.S. App. LEXIS 34998 (Fed. Cir. 1995).

In view of the arguments above, withdrawal of the rejection of Claims 1, 2, 5, 6, 8, 10 and 12 under 35 U.S.C. §103 is respectfully requested.

Claims 1, 3 and 4 are rejected under 35 U.S.C. §103 as unpatentable over Schofield et al. (Nature 330:644-646 (1987) or Weiss et al. (Proc. Nat'l. Acad. Sci. USA 85(1):573-576 (1988) in view of Kensil et al. and in further view of Schneerson et al. The is rejection is respectfully traversed. The deficiencies of the secondary and tertiary references have been discussed above and those remarks will not be repeated but are incorporated herein by reference. Turning now to the two primary references:

The Weiss et al. paper notes that $CD8^+$ T cells are required for protection and the immunization with irradiated sporozoites is impractical. It further notes that cellular immunity may be critical for an effective vaccine. In the discussion section the authors opine that a vaccine should probably induce both humoral and T-cell immunity but give no indication how this could be achieved. Likewise, Schofield et al. state the problem (the need for γ-IFN production) but fail to provide a solution. Neither of these references singly or in combination with the secondary or tertiary references suggest the claimed invention. The combination of references cited is insufficient to establish a prima facie case of obviousness for the legal reasoning mention above which is repeated here by reference.

In view of the remarks above withdrawal of the rejection of Claims 1, 3 and 4 under 35 U.S.C. §103 is respectfully requested.

Finally, Claims 1, 7 ,9 and 11 are rejected under 35 U.S.C. §103 as unpatentable over Cantrell et al.(U.S. Patent 4,877,611 in view of Kensil et al. This rejection is respectfully traversed. The Cantrell et al. reference suffers the same deficiency as did Schneerson et al. the compound taught is MPL not 3D-MPL. Its similarity to 3D-MPL is not relevant (See: In re Ochiai cited above). Furthermore, the reference only teaches MPL in combination with a bacterial

immunostimulant, there is no suggestion to combine it with a willow bark extract. The deficiencies in Kensil et al. discussed above are repeated here by reference.

For the factual and legal reasoning given above, withdrawal of the rejection of Claims 1, 7, 9 and 11 under 35 U.S.C. §103 is respectfully requested.

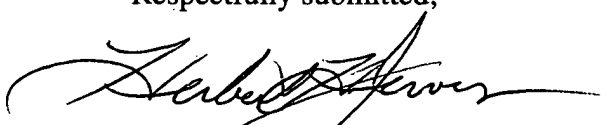
For the avoidance doubt, although both Cantrell et al. and Schneerson et al. fail to teach 3D-MPL 9and even if they did they clearly fail to suggest the claimed combination0, references to 3D-MPL do exist, as pointed out in the subject application at page 1, lines 9-12 or in U.S. Patent 4,912,094, a copy of which is enclosed. However, there is no suggestion that QS21 and 3D-MPL should be combined as co-adjuvants or that a greater than additive effect on CTL response often results when they are so used.

New Claims:

New Claims 13-18 have been added to more distinctly claim the subject matter of the instant invention. Support for these claims is found in the specification as filed.

Applicants believe all claims, 1-7 and 10-18, are in condition for allowance and such action is respectfully requested.

Respectfully submitted,



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